10/520143
PCT/EP 03/07127

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN
COMPLIANCE WITH
RULE 17.1(a) OR (b)

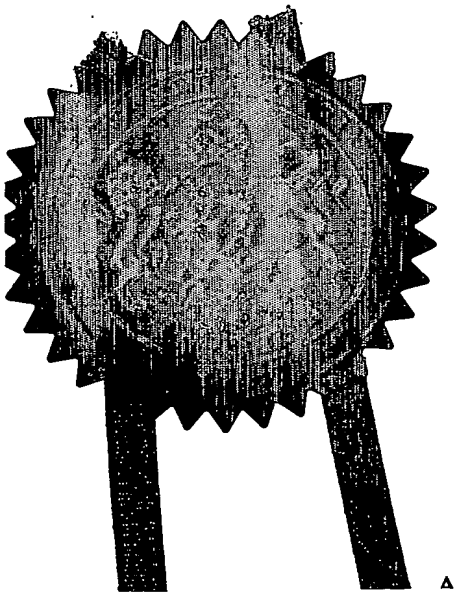
PCT/EP03/7127

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.



Signed Andrew Cregg

Dated 16 June 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

THE PATENT OFFICE
B
-3 JUL 2002
LONDON

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your Reference — **AP/PI4861**

2. **0215393.0** — 3 JUL 2002 — 04JUL02 E730750-1 D01030
P01/7700 0.00 0215393.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)*

GB 473587003

If the applicant is a corporate body, give the country/state of its corporation

4 Title of the invention — **CHEMICAL COMPOUNDS**

5 Name of your agent *(if you know one)* — **PETER I DOLTON**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY
CN925.1
980 GREAT WEST ROAD
BRENTFORD
MIDDLESEX
TW8 9GS, GB

Patents ADP number *(if you know it)* 8072555006

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	40
Claim(s)	3
Abstract	1
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

P. I. Dolton.

Signature PETER I DOLTON. 3 July 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY

020 8047 4420

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) Notes

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form

If you have answered "Yes" Patents Form 7/77 will need to be filed.

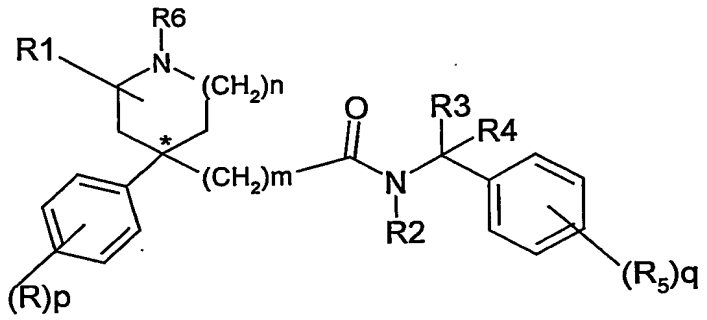
d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

Chemical Compounds

The present invention relates to piperazine derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

The present invention thus provides compounds of formula (I)



(I)

wherein

R represents halogen , C_{1-4} alkyl, trifluoromethyl or trifluoromethoxy;

R_1 represents hydrogen, halogen , cyano, C_{1-4} alkyl optionally substituted by halogen, cyano, C_{1-4} alkoxy;

R_2 represents hydrogen, or C_{1-4} alkyl;

R_3 and R_4 independently represent hydrogen, C_{1-4} alkyl or R_3 together with the R_4 represents C_{3-7} cycloalkyl;

R_5 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_6 represents hydrogen or $(CH_2)rR_7$;

R_7 represents hydrogen, C_{3-7} cycloalkyl, C_{1-4} alkoxy, amine, C_{1-4} alkylamine, $(C_{1-4}$ alkyl$)_2$amine, $OC(O)NR_9R_8$ or $C(O)NR_9R_8$;

R_9 and R_8 independently represent hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl;

m represents zero or an integer from 1 to 4;

n represents 1 or 2;

p is an integer from 1 to 3;

q are independently zero or an integer from 1 to 3;

r is an integer from 1 to 4;

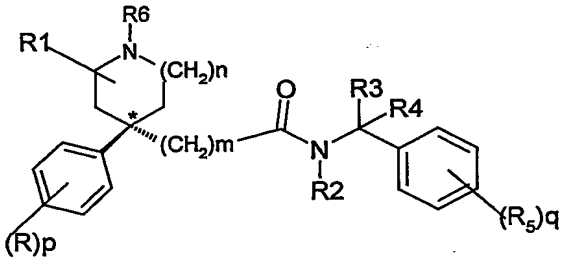
and pharmaceutically acceptable salts and solvates thereof.

Suitable pharmaceutically acceptable salts of the compounds of general formula (I) include acid addition salts formed with pharmaceutically acceptable organic or inorganic acids, for example hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonates), phosphates, trifluoroacetates, acetates, citrates, succinates, tartrates, lactates, malates, fumarates and maleates.

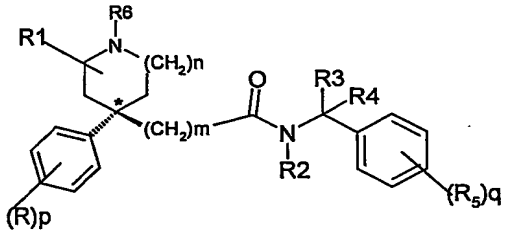
The solvates may, for example, be hydrates.

References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable acid addition salts and their pharmaceutically acceptable solvates.

It will be appreciated by those skilled in the art that the compounds of formula (I) provided that when n is 1 and R_1 is not hydrogen contain at least one chiral centre (namely the carbon atom shown as * in formula (I)) and may be represented by formula (1a) and (1b).



(1a)



(1b)

The wedge bond indicates that the bond is above the plane of the paper. The broken bond indicates that the bond is below the plane of the paper.

Further asymmetyric carbon atoms are possible in the compounds of formula (I) when R_3 and R_4 are not the same group.

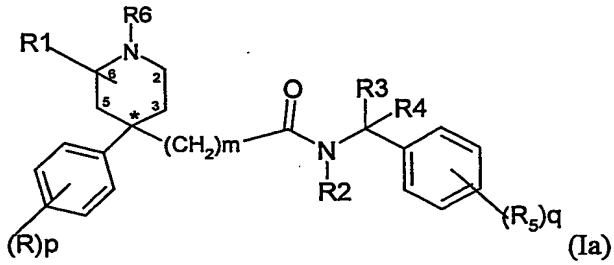
It is to be understood that all stereoisomeric forms including all enantiomers and mixtures thereof are encompassed within the scope of the present invention and the reference to compound of formula (I) include all stereisomeric forms unless otherwise stated.

The term C_{1-4} alkyl as used herein as a group or a part of the group refers to a straight or branched alkyl group containing from 1 to 4 carbon atoms; examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, 1 methylethyl or 2-methyl propyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

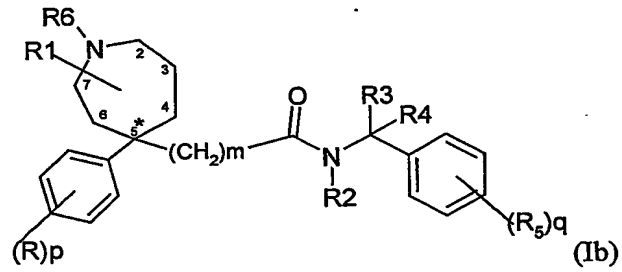
The term C_{3-7} cycloalkyl group means a non aromatic monocyclic hydrocarbon ring of 3 to 7 carbon atom such as, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.
The term C_{1-4} alkoxy group may be a straight chain or a branched chain alkoxy group, for example methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy or methylprop-2-oxy.

In the compounds of formula (I) wherein n is 1 the group R_1 may be in position 2, 3, 5 or 6 of the piperidine ring as represented in formula (Ia)



(Ia)

In the compounds of formula (I) wherein n is 2 the group R_1 may be in position 2, 3, 5, 6 or 7 of the ring as represented in formula (Ia).



(Ib)

R is preferably halogen (e.g. fluorine) and/or a C_{1-4} alkyl (e.g. methyl) group and p is preferably an integer from 1 to 2.

R_1 is preferably hydrogen, halogen (e.g. fluorine) or methyl .

R_2 is preferably hydrogen or methyl .

R_3 is preferably hydrogen or methyl .

R_4 is preferably hydrogen, methyl or together with R_3 is cyclopropyl.

R_5 is preferably trifluoromethyl, methyl , chlorine or fluorine atom and q is preferably an integer from 1 to 2.

Preferred compounds according to the invention are:
N-(3,5-Dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;
N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;
4-(4-Fluorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(4-Chlorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide;
4-(4-Fluorophenyl)-piperidine-4-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;
N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
and pharmaceutically acceptable salts thereof (e.g. hydrochloride)

The compounds of the invention are antagonists of tachykinin receptors, including substance P and other neurokinins, both in vitro and in vivo and are thus of use in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins.

Tachykinins are a family of peptides that share a common carboxyl-terminal sequence (Phe-X-Gly-Leu-Met-NH2). They are actively involved in the physiology of both lower and advanced lifeforms. In mammalian lifeforms the main tachykinins are subtance P (SP), Neurokinin A (NKA) and Neurokinin B (NKB) which act as neurotransmitters and neuromodulators. Mammalian tachykinins may contribute to the pathophysiology of a number of human diseases.
Three types of tachykinins receptors have been identified, namely NK1(SP-preferring), NK2 (NKA-preferring) and NK3 (NKB-preferring) which are widely distributed throughout the central nervous (CNS) and peripheral nervous system.

Particularly the compounds of the invention are antagonists of the NK1 receptor.

The compounds of the present invention also have activity as selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) and are thus of use in the treatment of conditions mediated by selective inhibition of the serotonin reuptake transporter protein.

Thus the compounds of the present invention combine dual activity as tachykinin antagonists, including substance P and other neurokinins, and as SSRIs. In particular, the compounds of the invention combine dual activity as NK1 receptor antagonists and as SSRIs.

NK_1-receptor binding affinity has been determined in vitro by measuring the compounds' ability to displace [3H] - substance P (SP) from recombinant human NK_1 receptors expressed in Chinese Hamster Ovary (CHO) cell membranes.
CHO cell membranes were prepared by using a modification of the method described by Beattie D.T. et al. (Br. J. Pharmacol, 116:3149-3157, 1995). Briefly, ligand binding was performed in 0.2 ml of 50 mM HEPES, pH 7.4, containing 3 mM $MnCl_2$, 0.02% BSA, 0.5 nM [^{3}H]-Substance P (30÷56 Ci/mmol, Amersham), a final membrane concentration of 20÷

30 µg of protein/ml, and the test compounds. The incubation proceeded at room temperature for 40 min and stopped by filtration. Non-specific binding was determined using excess of Substance P (1 µM) and represents about 6÷10% of the total binding.
Compounds of the invention were further characterised in a functional assay for the determination of their effect to inhibit the intracellular calcium increase induced by SP in Human-NK_1-CHO cells using FLIPR technology. Briefly, after 30min incubation with the cytoplasmic calcium indicator Fluo-4 AM (2µM), cells were washed and incubated in the absence or presence of three different concentrations of antagonist for 60min, at 37°C in Hank's balanced salts with 20mM Hepes, and then non-cumulative concentration-response curves of SP (2pM-300nM) was performed. The potency of the antagonist (pK_B value) was calculated from Schild's analysis.

The action of the compounds of the invention at the NK_1 receptor and/or serotonin transporter may be determined by using conventional animal models. Thus the ability to bind at the NK_1 receptor and/or serotonin transporter was determined using the guinea pig pup isolation calls model as described by Pettijohn, Psychol. Rep., 1979 and Rupniak et al., Neuropharmacology, 2000.

Human Serotonin Transporter (hSERT) binding affinity has been determined in vitro by the compounds' ability to displace [^{3}H]- Imipramine from human serotonin transporter expressed in Human Embryonic Kidney HEK293 cell membranes (Receptor Biology Inc.). For the binding reaction, 4 nM of [^{3}H]- Imipramine (703 GBq/mmol, Amersham) were incubated with 0.02 mg/ml of cell membrane and the compound to be tested at different concentrations (7 concentration points) in 50 mM Tris HCl, pH 7.5, 120 mM of NaCl and 5 mM KCl. The reaction was performed for 60 min at 4°C and was terminated by through GF/B Unifilter (pre-soaked in 0.5 % PEI) using a Cell Harvester (Packard). Scintillation fluid was added to each filtered spot and radioactivity was determined using a scintillation counter (TopCount (Packard)). Non-specific binding was determined using Imipramine (100µM) and represents about 5% of the total binding.
For the preferred compounds of the invention Human Serotonin Transporter binding affinity has been also determined in vitro by the compounds ability to displace [3H] paroxetine.
Competition experiments were conducted with duplicate determination for each point.
Msat601 software package was used to elaborate the competition binding data.
IC_{50} values were converted to K_i values using Cheng-Prusoff equation.

The inhibitory activity of the compounds at the rat serotonin transporter has been determined in vitro using rSERT-LLCPK cells (LLCPK cells tranfected with the rat SERT). The cells have been plated onto 96-well plates (60000 cells/well). After 24 hr, cells have been washed in uptake buffer (Hank's balanced salt solution + 20 mM Hepes) and pre-incubated for 10 min at RT with 50 µl of buffer containing the test compounds. 50 µl of 50 nM [3H] Serotonin (5HT) solution (final concentration: 25 nM [3H] 5HT) have been added and plates have been incubated for 7 min at RT, during which cells take up radiolabelled 5HT. Aspirating the solution and rapidly washing the cells with cold buffer has terminated the uptake.

The amount of radioactive 5HT incorporated in the cells has been then measured by adding the scintillation cocktail directly onto the cells and reading the plate in the Top Count. The data have been digitally processed to obtain the pIC50 values of the antagonists. The pKi values have been calculated using the Chen-Prusoff equation.

Compounds of the invention are useful in the treatment of CNS disorders and psychotic disorders, in particular in the treatment or prevention of depressive states and /or in the treatment of anxiety as defined in, but not restricted to, Diagnostic statistical of mental disorder (DSM) IV edition edit by American psychiatric association SM-IV and international classification Diseases 10 th revision (ICD10) .

Thus for example depressive states include Major Depressive Disorder (MDD), including bipolar depression, unipolar depression, single or recurrent major depressive episodes , recurrent brief depression, with or without psychotic features, catatonic features, melancholic features including anorexia, weight loss, atypical features, anxious depression, cyclothymic or postpartum onset.

Other mood disorders encompassed within the term major depressive disorders include dysthymic disorder with early or late onset and with or without atypical features, neurotic depression, post traumatic stress disorders and social phobia; dementia of the Alzheimer's type, with early or late onset, with depressed mood; vascular dementia with depressed mood; mood disorders induced by alcohol, amphetamines, cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics, anxiolytics and other substances; schizoaffective disorder of the depressed type; and adjustment disorder with depressed mood. Major depressive disorders may also result from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, etc.

The term anxiety includes anxiety disorders, such as panic disorders with or without agoraphobia, agoraphobia , phobias for example social phobias or agoraphobia, obsessive-compulsive disorder, stress disorders including post traumatic stress disorder generalised anxiety disorder , acute stress disorders and mixed anxiety-depression disorders.

Compounds of the invention are useful as analgesics. In particular they are useful in the treatment of traumatic pain such as postoperative pain; traumatic avulsion pain such as brachial plexus; chronic pain such as arthritic pain such as occurring in osteo-, rheumatoid or psoriatic arthritis; neuropathic pain such as post-herpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia, fibromyalgia, causalgia, peripheral neuropathy, diabetic neuropathy, chemotherapy-induced neuropathy, AIDS related neuropathy, occipital neuralgia, geniculate neuralgia, glossopharyngeal neuralgia, reflex sympathetic dystrophy, phantom limb pain; various forms of headache such as migraine, acute or chronic tension headache, temporomandibular pain, maxillary sinus pain, cluster headache; odontalgia; cancer pain; pain of visceral origin; gastrointestinal pain; nerve entrapment pain; sport's injury pain; dysmennorrhoea; menstrual pain; meningitis; arachnoiditis; musculoskeletal pain; low back pain e.g. spinal stenosis; prolapsed disc; sciatica; angina; ankylosing spondyolitis; gout; burns; scar pain; itch; and thalamic pain such as post stroke thalamic pain.

Compounds of the invention are also useful in the treatment of sleep disorders including dysomnia, insomnia, sleep apnea, narcolepsy, and circadian ritmic disorders.

Compounds of the invention are also useful in the treatment or prevention of the cognitive disorders. Cognitive disorders include dementia, amnestic disorders and cognitive disorders not otherwise specified.

Furthermore compounds of the invention are also useful as memory and/or cognition enhancers in healthy humans with no cognitive and/or memory deficit.

Compounds of the invention are also useful in the treatment of tolerance to and dependence on a number of substances. For example, they are useful in the treatment of dependence on nicotine, alcohol, caffeine, phencyclidine (phencyclidine like compounds), or in the treatment of tolerance to and dependence on opiates (e.g. cannabis, heroin, morphine) or benzodiazepines; in the treatment of cocaine, sedative ipnotic, amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) addiction or a combination thereof.

Compounds of the invention are also useful as anti-inflammatory agents. In particular they are useful in the treatment of inflammation in asthma, influenza, chronic bronchitis and rheumatoid arthritis; in the treatment of inflammatory diseases of the gastrointestinal tract such as Crohn's disease, ulcerative colitis, inflammatory bowel disease and non-steroidal anti-inflammatory drug induced damage; inflammatory diseases of the skin such as herpes and eczema; inflammatory diseases of the bladder such as cystitis and urge incontinence; and eye and dental inflammation.

Compounds of the invention are also useful in the treatment of allergic disorders, in particular allergic disorders of the skin such as urticaria, and allergic disorders of the airways such as rhinitis.

Compounds of the invention are also useful in the treatment or prevention of schizophrenic disorders including paranoid schizophrenia, disorganised schizophrenia, catatonic schizophrenia, undifferentiated schizophrenia, residual schizoprenia.

Compounds of the invention are also useful in the treatment of emesis, i.e. nausea, retching and vomiting. Emesis includes acute emesis, delayed emesis and anticipatory emesis. The compounds of the invention are useful in the treatment of emesis however induced. For example, emesis may be induced by drugs such as cancer chemotherapeutic agents such as alkylating agents, e.g. cyclophosphamide, carmustine, lomustine and chlorambucil; cytotoxic antibiotics, e.g. dactinomycin, doxorubicin, mitomycin-C and bleomycin; anti-metabolites, e.g. cytarabine, methotrexate and 5- fluorouracil; vinca alkaloids, e.g. etoposide, vinblastine and vincristine; and others such as cisplatin, dacarbazine, procarbazine and hydroxyurea; and combinations thereof; radiation sickness; radiation therapy, e.g. irradiation of the thorax or abdomen, such as in the treatment of cancer; poisons; toxins such as toxins caused by

metabolic disorders or by infection, e.g. gastritis, or released during bacterial or viral gastrointestinal infection; pregnancy; vestibular disorders, such as motion sickness, vertigo, dizziness and Meniere's disease; post-operative sickness; gastrointestinal obstruction; reduced gastrointestinal motility; visceral pain, e.g. myocardial infarction or peritonitis; migraine; increased intercranial pressure; decreased intercranial pressure (e.g. altitude sickness); opioid analgesics, such as morphine; and gastro-oesophageal reflux disease, acid indigestion, over-indulgence of food or drink, acid stomach, sour stomach, waterbrash/regurgitation, heartburn, such as episodic heartburn, nocturnal heartburn, and meal-induced heartburn and dyspepsia.

Compounds of the invention are also useful in the treatment of gastrointestinal disorders such as irritable bowel syndrome; skin disorders such as psoriasis, pruritis and sunburn; vasospastic diseases such as angina, vascular headache and Reynaud's disease; cerebral ischeamia such as cerebral vasospasm following subarachnoid haemorrhage; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders related to immune enhancement or suppression such as systemic lupus erythematosus and rheumatic diseases such as fibrositis; and cough.
The compounds of the invention are also useful in premenstrual dysphoric disorder (PMDD), in chronic fatigue syndrome and Multiple sclerosis.

Compounds of the invention have been found to exhibit anxiolytic and antidepressant activity in conventional tests. For example in Guinea pig pups separation-induced vocalisations (Molewijk et al., 1996).

The invention therefore provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in therapy, in particular in human medicine.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of serotonin reuptake.

There is also provided as a further aspect of the invention the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.
In a further aspect there is provided the use of a compounds of formula(I) or a pharmaceutically acceptable salt or solvate thereof in the preparation of a medicament for use in the treatment of depression and /or anxiety.

In an alternative or further aspect there is provided a method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein comprising administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In a further aspect of the present invention is provided a method for the treatment of a mammal, including man, in particular in the treatment of depression and /or anxiety which method comprises administration of an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.
It will be appreciated that reference to treatment is intended to include prophylaxis as well as the alleviation of established symptoms.
Compounds of formula (I) may be administered as the raw chemical but the active ingredient is preferably presented as a pharmaceutical formulation.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one compound of formula (I) or a pharmaceutically acceptable salt thereof and formulated for administration by any convenient route. Such compositions are preferably in a form adapted for use in medicine, in particular human medicine, and can conveniently be formulated in a conventional manner using one or more pharmaceutically acceptable carriers or excipients.

Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the composition may take the form of tablets or formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

The compounds of the invention may be formulated for topical administration in the form of ointments, creams, gels, lotions, pessaries, aerosols or drops (e.g. eye, ear or nose drops). Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Ointments for administration to the eye may be manufactured in a sterile manner using sterilised components.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

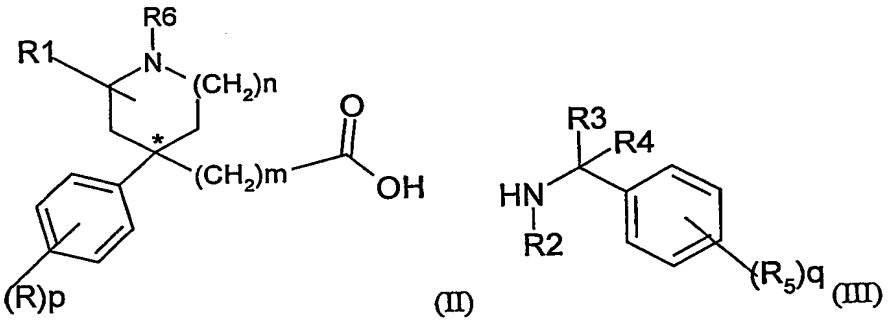
For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

A proposed dose of the compounds of the invention is 1 to about 1000mg per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient and the precise dosage will be ultimately at the discretion

of the attendant physician or veterinarian. The dosage will also depend on the route of administration and the particular compound selected.
Thus for parenteral administration a daily dose will typically be in the range of 1 to about 100 mg, preferably 1 to 80 mg per day. For oral administration a daily dose will typically be within the range 1 to 300 mg e.g. 1 to 100 mg.

Compounds of formula (I), and salts and solvates thereof, may be prepared by the general methods outlined hereinafter. In the following description, the groups R, R_1 R_2, R_3, R_4, R_5, , m , n, p and q have the meaning as previously defined for compounds of formula (I) unless otherwise stated.

Compounds of formula (I) may be prepared by reaction of an activated derivative of the carboxylic acid (II), wherein R_6 is nitrogen protecting group or (CH2)rR_7 , with amine (III)

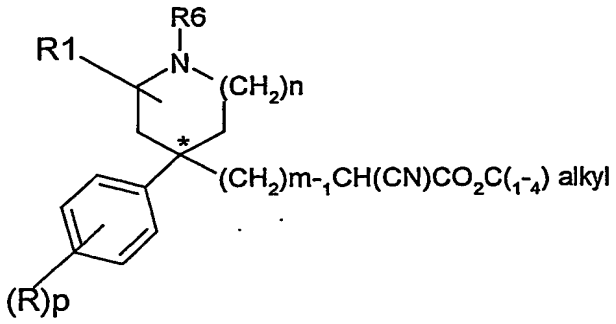


wherein R_2 is C_{1-4} alkyl or nitrogen protecting group, followed where necessary by removal of any nitrogen protecting group.

Suitable activated derivatives of the carboxyl group include the acyl halide, mixed anhydride, activated ester such as thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole or dicyclohexylcarbodiimide.
The reaction is preferably carried out in an aprotic solvent such as hydrocarbon, halohydrocarbon such as dichloromethane or an ether such as tetrahydrofuran.

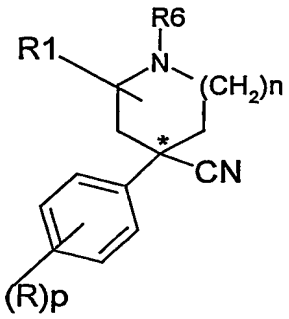
The activated derivatives of the carboxylic acid (II) may be prepared by conventional means. A particular suitable activated derivative for use in this reaction is O-(Benzotriazol-1-yl) – N,N,N',N'-tetramethyluronium tetrafluoroborate.

Compounds of formula (II), wherein m is an integer from 1 to 4, may be prepared by reaction of a cyano derivative (IV) with a acid such as for example concentrated sulfuric acid. The reaction is conveniently carried out in a solvent such as acetic acid and heating the reaction mixture up to 150° .



(IV)

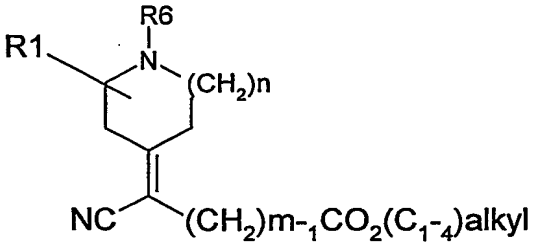
Compounds of formula (III), wherein m is zero , may be prepared by hydrolysis of a cyano derivative (V) in the presence of a base such as alkaline base (i.e potassium hydroxide).



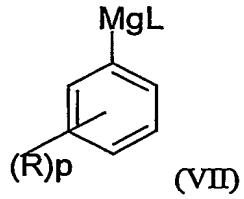
(V)

The reaction is suitable carried out in aqueous solvent and with heating .

Compounds of formula (IV) may be prepared by reaction of a compound of formula (VI) with a compound of formula (VII) , wherein L is a halogen group (i.e bromine).



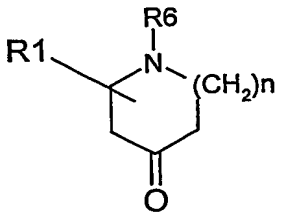
(VI)



(VII)

The reaction conveniently takes place in an aprotic solvent such as a hydrocarbon (i.e toluene) and at a temperature within the range 0-25°C.

Compounds of formula (VI) may be prepared by reaction of a compounds of formula (VIII) with a cyano derivative (IX).



(VIII)

$CN(CH_2)mCO_2C(_{1-4})alkyl$ (IX)

Compounds of formulae (V) and (VIII) may be prepared with analogous method to those used for known compounds. Thus compounds of formula (V) may be prepared according to the procedure described in Cammack et al., Heterocyclic 23,73 (1986).

Compounds of formula(VIII) may be prepared according to the procedure described in WO 2001/000206.

When R_6 and/or R_2 are a nitrogen protecting group, examples of suitable groups include alkoxycarbonyl e.g. t-butoxycarbonyl, benzyloxycarbonyl, arylsulphonyl e.g. phenysulphonyl or 2-trimethylsilylethoxymethyl.

Protection and deprotection may be effected using conventional techniques such as those described in "Protective Groups in Organic Synthesis 2nd Ed." by T.W. Greene and P. G. M. Wuts (John Wiley and Sons, 1991) and as described in the examples hereinafter.

Where it is desired to isolate a compound of formula (I) as a salt, for example a pharmaceutically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate amount of suitable acid and in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an ester (e.g. ethyl acetate) or an ether (e.g. diethyl ether, *tert*-butylmethyl ether or tetrahydrofuran).

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Buchi m.p. apparatus and are uncorrected. R.T. or r.t. refer to room temperature.

Infrared spectra (IR) were measured in chloroform or nujol solutions on a FT-IR instrument. Proton Magnetic Resonance (NMR) spectra were recorded on Varian instruments at 400 or 500 MHz, chemical shifts are reported in ppm (δ) using the residual solvent line as internal standard. Splitting patterns are designed as s, singlet; d, double; t, triple; q, quartet; m, multiplet; b, broad. Mass spectra (MS) were taken on a VG Quattro mass spectrometer. Optical rotations were determined at 20°C with a Jasco DIP360 instrument (l=10 cm, cell volume = 1 mL, λ = 589 nm). Flash silica gel chromatography was carried out over silica gel 230-400 mesh supplied by Merck AG Darmstadt, Germany. T.l.c. refers to thin layer chromatography on 0.25 mm silica gel plates (60F-254 Merck) and visualized with UV light. Solutions were dried over anhydrous sodium sulphate.

Methylene chloride was redistilled over calcium hydride and tetrahydrofuran was redistilled over sodium.

The following abbreviation are used in the text: AcOEt = ethyl acetate, CH = cyclohexane, DCM = methylene chloride, DIPEA = N,N-diisopropylethylamine, DMF = N,N'-

dimethylformamide, Et2O = diethyl ether, EtOH = ethanol, MeOH = methanol TEA = triethylamine, THF = tetrahydrofuran.

Intermediate 1

4-[(1-Cyano-1-ethoxycarbonyl)-methylene]-piperidine-1-carboxylic acid *tert*-butyl ester

Method A

A round bottom flask equipped with a Dean Stark apparatus was charged with *tert*-butyl-4-oxo-1-piperidine carboxylate (1.0 g), ethyl cyanoacetate (0.587 mL), ammonium acetate (0.193 g) and acetic acid (0.286 mL) in anhydrous benzene (20 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (20 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic extracts were washed with a 1M sodium hydroxide solution (10 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (1.5 g) as a yellow oil.

Method B

Ethyl cyanoacetate (13.9 mL), ammonium acetate (4.64 g) and acetic acid (6.9 mL) were added, under a Nitrogen atmosphere, to a solution of *tert*-butyl-4-oxo-1-piperidine carboxylate (20 g) in anhydrous toluene (200 mL) in a round bottom flask equipped with a Dean Stark apparatus. The mixture was heated to 110°C for 2 hours, then to 85°C overnight and finally to 130°C for 4 hours. The mixture was allowed to cool to r.t. and washed with 1M sodium hydroxide solution, water and brine. The organic layer was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (15.54 g) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, Rf=0.35 (detection with ninhydrine).

IR (nujol, cm^{-1}): 2229 (C≡N), 1720 and 1694 (C=O).

NMR ($CDCl_3$): δ (ppm) 4.29 (q, 2H); 3.61 (t, 2H); 3.55 (t, 2H); 3.13 (t, 2H); 2.78 (t, 2H); 1.49 (s, 9H); 1.36 (t, 3H).

MS (ES/+): m/z=295 $[M+H]^+$.

Intermediate 2

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of intermediate 1 (1.5 g) in anhydrous toluene (15 mL) were dropped over 30 minutes into a solution of 4-fluorophenyl magnesium bromide (2M in Et2O – 6.1 mL) in anhydrous Et2O (50 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and left at this temperature for 2 days. The mixture was treated with 3N sulfuric acid solution (5 mL), water (30 mL) and AcOEt (10 mL). The layers were separated and the aqueous phase was extracted with further AcOEt (2 x 30 mL). The

combined organic layers were washed with a saturated sodium hydrogen carbonate (60 mL) and water (60 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.448 g) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, Rf=0.2 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.31 (dd, 2H); 7.06 (t, 2H); 3.95 (q, 2H); 3.87 (bs, 2H); 3.54 (t, 1H); 2.85 (bt, 2H); 2.53 (dt, 2H); 1.9 (m, 2H); 1.4 (s, 9H); 1.02 (t, 3H).

MS (ES/+): m/z=391 $[MH]^+$.

Intermediate 3

4-Carboxymethyl-(4-fluoro-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester (

A mixture of intermediate **2** (0.448 g) in acetic acid (2 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (50 mL). Then, di-tert-butyl-dicarbonate (500 mg) was added and the resulting mixture was stirred at r.t. for 5 hours. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (210 mg) as a pale yellow foam.

T.l.c.: CH/AcOEt 1:1, Rf=0.25 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 11.78 (bs, 1H); 7.4 (dd, 2H); 7.15 (t, 2H); 3.45 (m, 2H); 3.11 (m, 2H); 2.54 (s, 2H); 2.04 (m, 2H); 1.89 (m, 2H); 1.37 (s, 9H).

Intermediate 4

4-{[(3,5-Dichlorobenzyl)methylcarbamoyl]methyl}-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl

3,5-Dichlorobenzyl-methylamine (37 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (37 mg) and 1-hydroxybenzotriazole (26 mg) were added to a solution of intermediate **3** (60 mg) in anhydrous DMF (2 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL), 0.005M hydrochloric acid solution (15 mL) and a saturated sodium hydrogen carbonate solution (15 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (80 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.35 (detection with ninhydrine).

NMR (d_6-DMSO – 70°C): δ (ppm) 7.37 (m, 3H); 7.03 (m, 4H); 4.28 (bs, 2H); 3.48 (m, 2H); 3.12 (m, 2H); 2.71 (bs, 2H); 2.57 (s, 3H); 2.2-1.9 (m, 4H); 1.38 (s, 9H).

Intermediate 5

3-Fluoro-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester

Trimethylsilyl trifluoromethanesulfonate (2.17 mL) was added to a solution of *tert*-butyl-4-oxo-1-piperidine carboxylate (2.0 g) and TEA (3.34 mL) in anhydrous DCM (20 mL) previously cooled to -30°C under a Nitrogen atmosphere. The mixture was stirred at this temperature for 1 hour, then it was quickly treated with cold saturated sodium hydrogen carbonate solution (20 mL). The layers were separated and the the organic phase was dried and concentrated *in vacuo* to give 1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-4-pyridinyl-trifluoromethanesulfonate as a yellow oil, which was dissolved in anhydrous acetonitrile (80 mL) and the resulting solution was treated with Selectfluor (3.89 g). The mixture was stirred at r.t. for 1 hour, then it was concentrated *in vacuo* and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with a saturated sodium hydrogen solution (30 mL), dried and concentrated *in vacuo* to a residue, which was purified by chromatography on neutral Alumina Brochmann type 1 (initially AcOEt then AcOEt/MeOH 95:5) to give the title compound (0.99 g) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.3 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 5.08 (dd, 1H); 4.32 (bm, 1H); 4.0 (bm, 1H); 3.19 (m, 2H); 2.56 (m, 1H); 2.36 (m, 1H); 1.43 (s, 9H).

Intermediate 6

4-(1-Cyano-1-ethoxycarbonyl-methylene)-3-fluoro-piperidine-1-carboxylic acid *tert*-butyl ester

A round bottom flask equipped with a Dean Stark apparatus was charged with intermediate 5 (0.99 g), ethyl cyanoacetate (0.534 mL), ammonium acetate (0.176 g) and acetic acid (0.261 mL) in anhydrous benzene (20 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (20 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic extracts were washed with a 1M sodium hydroxide solution, dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.696 g – cis/trans mixture) as a yellow oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.45 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 6.49 and 5.55 (2bd, 1H); 4.54 (bm, 1H); 4.34 (bm, 3H); 3.72 (m, 1H); 3.12 (bm, 1H); 2.9 (bm, 1H); 2.74 (m, 1H); 1.49 (s, 9H); 1.38 (t, 3H).

Intermediate 7

4-(1-Cyano-1-ethoxycarbonyl-methyl)-3-fluoro-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of intermediate **6** (0.696 g) in anhydrous toluene (5 mL) was dropped over 30 minutes into a solution of 4-fluorophenyl magnesium bromide (2M in Et2O – 2.67 mL) in anhydrous Et2O (15 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and stirred at this temperature overnight. The mixture was treated with 3N sulfuric acid solution (3 mL), water (10 mL) and AcOEt (25 mL). The layers were separated and the aqueous phase was extracted with further AcOEt (2 x 30 mL). The combined organic layers were washed with a saturated sodium hydrogen carbonate (60 mL) and water (60 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.383 g) as a yellow oil.

T.l.c.: CH/AcOEt 8:2, Rf=0.27 (detection with ninhydrine).
NMR ($CDCl_3$): δ (ppm) 7.5-6.8 (m, 4H); 4.8 (bm, 2H); 4.5-3.5 (bm; 3H); 3.85 (s, 1H); 3.2-2.4 (bm, 2H); 2.2 (bm, 2H); 1.4 (s, 9H); 1.05 (2t, 3H).

Intermediate 8

4-Carboxymethyl-3-fluoro-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate 7 (0.383 g) in acetic acid (2 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 3M sodium hydroxide solution (50 mL). Then, di-*tert*-butyl-dicarbonate (409 mg) was added and the resulting mixture was stirred at r.t. overnight. It was cooled to 0°C and treated with 3M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (96 mg) as a pale yellow oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.5 (detection with ninhydrine).
NMR (d_6-DMSO): δ (ppm) 11.89 (bs, 1H); 7.46 (dd, 2H); 7.16 (t, 2H); 5.36 (dd, 1H); 3.96 (bm, 1H); 3.75 (bm, 1H); 3.2-2.6 (bm, 3H); 2.5 (m, 1H); 2.36 (bd, 1H); 1.93 (bm, 1H); 1.38 (s, 9H).

Intermediate 9

4-{[(3,5-Dichlorobenzyl)-methylcarbamoyl]-methyl}-3-fluoro-4-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

3,5-Dichlorobenzyl-methylamine (53 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (53 mg) and 1-hydroxybenzotriazole (38 mg) were added to a solution of intermediate 8 (90 mg) in anhydrous DMF (4 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (20 mL) and washed with water

(15 mL), 0.005M hydrochloric acid solution (15 mL) and a saturated sodium hydrogen carbonate solution (15 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (62 mg) as a white foam.

T.l.c.: CH/AcOEt 7:3, Rf=0.30 (detection with ninhydrine).

NMR (d_6-DMSO – 60°C): δ (ppm) 7.42 (m, 3H); 7.08 (m, 2H); 6.98 (bs, 2H); 5.58-5.5 (bd, 1H); 4.28 (m, 2H); 3.99 (m, 1H); 3.75 (bm, 1H); 3.0 (bm, 1H); 2.89 (d, 1H); 2.79 (bm, 1H); 2.68 (d, 1H); 2.64-2.57 (2bs, 1H); 2.4 (bm, 1H); 2.04-1.98 (2bm, 1H); 1.38 (s, 9H).

Intermediate 10

3,4-Dimethoxybenzyl chloride

A solution of 3,4-dimethoxy-benzyl alcohol (1.5 g) in anhydrous DCM (5 mL) was dropped into a solution of thionyl chloride (1.3 mL) in anhydrous DCM (6 mL) under a Nitrogen atmosphere. The solution was heated to reflux for 1 hour, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (1.63 g) as a white solid.

T.l.c.: CH/AcOEt 6:4, R=0.63.

NMR ($CDCl_3$): δ (ppm) 7.94 (dd, 1H); 6.92 (d, 1H); 6.83 (d, 1H); 4.57 (s, 2H); 3.9 (s, 3H); 3.89 (s, 3H).

MS (EI/+): m/z=186 $[MH]^+$.

Intermediate 11

Bis-(2-hydroxyethyl)-3,4-diemthoxybenzylamine

Intermediate **10** (1.38 g) was added to a mixture of diethanolamine (0.71 mL) and potassium carbonate (1.12 g) in anhydrous toluene (13 mL) previously heated to 60°C under a Nitrogen atmosphere. The resulting mixture was heated to reflux for 1 hour, then allowed to cool to r.t., filtered off and the organic phase was concentrated *in vacuo* to give the title compound (1.87 g) as a yellow oil.

NMR ($CDCl_3$): δ (ppm) 6.85 (dd, 1H); 6.8 (d, 2H); 3.9 (2s, 6H); 3.6 (s, 2H); 3.55 (dd, 4H); 2.6-2.7 (d, 4H).

Intermediate 12

Bis-(2-chloroethyl)-3,4-dimethoxybenzylamine

A solution of thionyl chloride (1.37 mL) in anhydrous DCM (7 mL) was dropped into a solution of intermediate **10** (1.85 g) in anhydrous DCM (11 mL) under a Nitrogen atmosphere. The solution was heated to reflux for 3 hour, then allowed to cool to r.t. and

concentrated *in vacuo*. The residue was triturated from Et2O to give the title compound (2.08 g) as a whitish solid.

NMR ($CDCl_3$): δ (ppm) 7.6 (s, 1H); 6.9 (d, 1H); 6.8 (d, 1H); 4.25 (s, 2H); 4.1-3.95 (m, 4H); 3.92 (s, 3H); 3.85 (s, 3H); 3.5-3.4 (m, 4H).

Intermediate 13

1-(3,4-Dimethoxybenzyl)-4-(4-fluorophenyl)-4-cyanopiperidine hydrochloride

Intermediate **12** (1.41 g) and hexadecyltributyl phosphonium bromide (104 mg) were added to a mixture of 4-fluoroacetonitrile (0.488 mL) in a 50% sodium hydroxide solution (10 mL). The mixture was heated to reflux for 1 hour, then it was allowed to cool to r.t , then a 6M hydrochloric acid solution was added until acidic pH and the mixture was extracted with AcOEt (3 x 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to a residue, which was triturated with AcOEt to give the title compound (1.017 g) as a whitish solid.

IR (nujol, cm-1): 1609 (C=C).

NMR (d_6-DMSO): δ (ppm) 10.72 (bs, 1H); 7.56 (m, 2H); 7.35 (m, 3H); 7.11 (d, 1H); 7.02 (d, 1H); 4.37 (d, 2H); 3.8 (s, 3H); 3.77 (s, 3H); 3.52 (bm, 2H); 3.18 (bm, 2H); 2.46 (bm, 4H).

MS (ES/+): m/z=355 $[MH\text{-}HCl]^+$.

Intermediate 14

4-(4-Fluorophenyl)-4-cyanopiperidine

Intermediate **13** (150 mg) was treated with a 3M potassium hydroxide solution (20 mL) and extracted with AcOEt (2 x 20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give 1-(3,4-dimethoxybenzyl)-4-(4-fluorophenyl)-4-cyanopiperidine (136 mg). Cerium ammonium nitrate (842 mg) was added to a solution of this compound (136 mg) in acetonitrile (4.3 mL) and water (0.48 mL). The mixture was stirred at r.t. for 21 hour, then it was concentrated *in vacuo*. The residue was triturated with a 20% sodium hydroxide solution (20 mL), the inorganic salts were filtered off and the aqueous phase was extracted with AcOEt (4 x 25 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (AcOEt/MeOH 6:4 + 1% TEA) to give the title compound (46 mg) as a yellow oil.

Method B:

A mixture of intermediate **26** (1.36 g) and 10% palladium over charcoal (0.42 g) in EtOH (12.8 mL) and acetic acid (0.13 mL) was hydrogenated at 4.5 atm. for 4 hours. The mixture was filtered over celite and the solution was concentrated *in vacuo*. The residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the title compound (0.71 g) as a yellow oil.

T.l.c.: AcOEt/MeOH 8:2, Rf=0.09 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 7.56 (m, 2H); 7.27 (t, 2H); 3.04 (m, 2H); 2.8 (m, 2H); 2.01 (m, 2H); 1.84 (m, 2H).

MS (ES/+): m/z=205 $[MH]^+$.

Intermediate 15

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid hydrochloride

A solution of intermediate **14** (100 mg) in a 3M potassium hydroxide solution (6.6 mL) was heated to reflux for 21 hours. The solution was allowed to cool to r.t. and acidified with conc. hydrochloric acid until pH=2. The solid obtained was filtered off and the aqueous layer was concentrated *in vacuo*. The residue was treated with MeOH; the alcoholic solution was filtered off and concentrated *in vacuo* to give the title compound (106 mg) as a brown solid.

NMR (d_6-DMSO): δ (ppm) 13.0 (bs, 1H); 8.85-8.95 (bm, 2H); 7.55-7.45 (m, 2H); 7.3-7.2 (m, 2H); 3.35 (m, 2H); 2.95-2.85 (bm, 2H); 2.5 (m, 2H); 2.05 (m, 2H).

MS (ES/+): m/z=224 $[MH-HCl]^+$.

Intermediate 16

1-(*tert*-Butoxycarbonyl)-4-(4-fluorophenyl)-piperidine-4-carboxylic acid

TEA (0.33 mL) and di-*tert*-butyl-dicarbonate (0.52 g) were added to a solution of intermediate **15** (0.56 g) in anhydrous DMF (21 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 16 hours, then AcOEt was added (50 mL) and the mixture was washed with 2.5% hydrochloric acid solution (30 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (0.683 g) as a brown oil.

T.l.c.: DCM/MeOH 94:6, Rf=0.62 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.45-7.35 (m, 2H); 7.15-7.05 (m, 2H); 4.35-4.2 (bm, 2H); 3.25-3.1 (m, 2H); 2.07-2.02 (m, 2H); 1.92-1.84 (m, 2H); 1.45 (s, 9H).

Intermediate 17

[(3,5-Bis-trifluoromethylbenzyl)-methylcarbamoyl]-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (53 mg), 1-hydroxybenzotriazole (37 mg), intermediate **16** (80 mg) and TEA (35 μL) in anhydrous DCM (3 mL) was stirred at r.t. for 20 hours under a Nitrogen atmosphere, then TEA (90 μL) and 3,5-bis(trifluorobenzyl)-methylamine (182 mg) were added. The mixture was stirred at r.t. for 48 hours, then it was washed with a 5% sodium hydrogen carbonate solution (2 x 5 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (36.7 mg) as a white solid.

T.l.c.: CH/AcOEt 6:4, Rf=0.48.

IR (nujol, cm^{-1}): 1678 (C=O), 1614 (C=C).
NMR (d_6-DMSO – 70°C): δ (ppm) 7.92 (bs, 1H); 7.74 (bs, 2H); 7.32 (m, 2H); 7.13 (t, 2H); 4.64 (bs, 2H); 3.76 (m, 2H); 3.12 (m, 2H); 2.61 (s, 3H); 2.35 (m, 1H); 1.83 (m, 1H); 1.41 (s, 9H).
MS (ES/+): m/z=563 $[MH]^+$.

Intermediate 18

4-(4-Chlorophenyl)-4-cyano-1-(3,4-dimethoxybenzyl)-piperidine hydrochloride

Intermediate **12** (2 g) and hexadecyltributyl phosphonium bromide (147.2 mg) were added to a mixture of 4-chlorophenylacetonitrile (0.88 g) in a 50% sodium hydroxide solution (8.7 mL). The mixture was heated to reflux for 1 hour, then it was allowed to cool to r.t.. A 6M hydrochloric acid solution was added until acidic pH and the mixture was extracted with AcOEt (3 x 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give the title compound (1.75 g) as a whitish solid.
NMR (d_6-DMSO): δ (ppm) 10.52 (bs, 1H); 7.8-7.7 (m, 4H); 7.35 (m, 1H); 7.21-7.15 (d, 1H); 7.05-7.0 (d, 1H); 4.37 (d, 2H); 3.8 (s, 6H); 3.77-3.6 (m, 2H); 3.3 (s, 3H); 3.2-3.05 (bm, 2H); 2.75-2.55 (bm, 2H); 2.46 (bm, 2H).

Intermediate 19

4-(4-Chlorophenyl)-4-cyanopiperidine

Intermediate **18** (1.5 g) was treated with a 3M potassium hydroxide solution (100 mL) and extracted with AcOEt (2 x 80 mL). The combined organic extracts were dried and concentrated *in vacuo* to give 4-(4-chlorophenyl)-4-cyano-1-(3,4-dimethoxybenzylpiperidine (1.3 g). Cerium ammonium nitrate (7.69 g) was added to a solution of this compound (1.3 g) in acetonitrile (40 mL) and water (4.4 mL). The mixture was stirred at r.t. for 15 hours, then it was concentrated *in vacuo*. The residue was triturated with a 20% sodium hydroxide solution (80 mL), the inorganic salts were filtered off and the aqueous phase was extracted with AcOEt (4 x 100 mL). The combined organic extracts were washed with brine (50 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (AcOEt/MeOH 6:4 + 1% TEA) to give the title compound (210 mg) as a brown solid.
T.l.c.: AcOEt/MeOH 6:4 + 1% TEA, Rf=0.22 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 7.5 (m, 4H); 3.25-3.1 (m, 3H); 2.95-2.85 (m, 2H); 2.2-2.1 (bm, 2H); 2.05-1.97 (bm, 2H).
MS (ES/+): m/z=221 $[MH]^+$.

Intermediate 20

4-(4-Chlorophenyl)-piperidine-4-carboxylic acid hydrochloride

A solution of intermediate **19** (177 mg) in a 3M potassium hydroxide solution (10.7 mL) was heated to reflux for 21 hours. The solution was allowed to cool to r.t. and acidified with conc. hydrochloric acid until pH=2. The solid obtained was filtered off; the aqueous layer was concentrated *in vacuo* to half volume and cooled to 0°C. The solid precipitated was filtered off to give the title compound (147 mg) as a brown solid.

IR (nujol, cm^{-1}): 1712 (C=O).

NMR (d_6-DMSO): δ (ppm) 13.1 (bs, 1H); 8.62 (bs, 2H); 7.47 (m, 2H); 7.4 (m, 2H); 3.23 (m, 2H); 2.94 (m, 2H); 2.49 (m, 2H); 2.05 (m, 2H).

MS (ES/+): m/z=240 $[MH-HCl]^+$.

Intermediate 21

1-(*tert*-Butoxycarbonyl)-4-(4-chlorophenyl)-piperidine-4-carboxylic acid

DIPEA (0.1 mL) and di-*tert*-butyl-dicarbonate (126.3 mg) were added to a solution of intermediate **20** (145 mg) in anhydrous DMF (5.3 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 24 hours, then AcOEt was added (20 mL) and the mixture was washed with 1M hydrochloric acid solution (20 mL). The organic phase was dried and concentrated *in vacuo* to give the title compound (145 mg) as a brown oil.

T.l.c.: DCM/MeOH 94:6, Rf=0.5 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.4-7.25 (m, 2H); 7.0-6.95 (m, 2H); 4.15-4.0 (bm, 2H); 3.1-2.9 (m, 2H); 2.07-2.6 (m, 2H); 1.92-1.8 (m, 2H); 1.45 (s, 9H).

Intermediate 22

[(3,5-Bis-trifluoromethylbenzyl)-methylcarbamoyl]-(4-chlorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (91 mg), 1-hydroxybenzotriazole (64 mg), intermediate **21** (145 mg) and TEA (66 µL) in anhydrous DCM (5 mL) was stirred at r.t. for 12 hours under a Nitrogen atmosphere, then TEA (160 µL) and 3,5-bis(trifluorobenzyl)-methylamine (315 mg) were added. The mixture was stirred at r.t. for 48 hours, then it was washed with a 5% sodium hydrogen carbonate solution (2 x 5 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (18 mg) as a white solid.

T.l.c.: CH/AcOEt 6:4, Rf=0.45.

NMR ($CDCl_3$): δ (ppm) 7.85 (bm, 1H); 7.65 (s, 1H); 7.6-7.5 (m, 1H); 7.39-7.3 (d, 2H); 7.2-7.15 (d, 2H); 4.63-4.5 (bm, 2H); 4.0-3.85 (m, 2H); 3.26 (m, 2H); 3.0 (m, 2H); 2.65 (s, 3H); 2.35 (m, 2H); 1.45 (s, 9H).

Intermediate 23

[(3,5-Dichlorobenzyl)-methylcarbamoyl]-(4-fluorophenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (162 µL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (126 mg) were added to a solution of intermediate **16** (100 mg) in anhydrous DMF (12 mL) under a Nitrogen atmosphere. After stirring for 1 hour, 3,5-dichlorobenzyl-methylamine hydrochloride (140 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (82 mg) as a colourless oil.

T.l.c.: AcOEt, Rf=0.72.

IR (nujol, cm^{-1}): 1678 (C=O), 1614 (C=C).

NMR (d_6-DMSO – 70°C): δ (ppm) 7.49 (m, 1H); 7.3 (m, 4H); 7.15 (bm, 2H); 4.44 (bs, 2H); 3.79 (bd, 2H); 3.07 (bm, 2H); 2.54 (bs, 3H); 2.31 (bd, 2H); 1.77 (bt, 2H); 1.39 (s, 9H).

MS (ES/+): m/z=495 $[MH]^+$.

Intermediate 24

Bis-(2-hydroxyethyl)-benzylamine

Benzylbromide (13.91 mL) was added to a mixture of diethanolamine (11 mL) and potassium carbonate (17.79 g) in anhydrous toluene (190 mL) previously heated to 60°C under a Nitrogen atmosphere. The resulting mixture was heated to reflux for 1 hour, then further benzylbromide (6.95 mL) was added, and the mixture refluxed for further 3 hours. The mixture was allowed to cool to r.t., filtered and the organic phase was concentrated *in vacuo* to give the title compound (22.8 g) as a yellow oil.

T.l.c.: AcOEt/MeOH 9:1, Rf=0.58 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.5-7.1 (m, 5H); 4.2 (bm, 1H); 3.67 (s, 2H); 3.55 (t, 4H); 3.43 (bm, 1H); 2.64 (t, 4H).

Intermediate 25

Bis-(2-chloroethyl)-benzylamine

A solution of thionyl chloride (20.49 mL) in anhydrous DCM (300 mL) was dropped into a solution of intermediate **24** (22.8 g) under a Nitrogen atmosphere. The solution was heated to reflux for 5 hour, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was triturated from AcOEt to give the title compound (23.81 g) as a whitish solid.

NMR ($CDCl_3$): δ (ppm) 7.7 (m, 2H); 7.45 (m, 3H); 4.4 (s, 2H); 4.1-4.0 (m, 4H); 3.55-3.45 (t, 4H).

Intermediate 26

1-Benzyl-4-(4-fluorophenyl)-4-cyanopiperidine

Intermediate **25** (23.81 g) and hexadecyltributyl phosphonium bromide (2.15 g) were added to a mixture of 4-fluoroacetonitrile (10.14 mL) in a 50% sodium hydroxide solution (128 mL). The mixture was heated to reflux for 2 hours, then it was allowed to cool to r.t . A 6M hydrochloric acid solution was added until acidic pH and the mixture was extracted with AcOEt (3 x 100 mL). The combined organic extracts were dried and concentrated *in vacuo*. The solid so obtained was dissolved in a 1% sodium hydroxide solution and extracted with DCM. The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 1:1) to give the title compound (8.99 g) as a brown oil.

T.l.c.: CH/AcOEt 4:6, Rf=0.59 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.45 (m, 2H); 7.3 (m, 5H); 7.1-7.0 (t, 2H); 3.6 (s, 2H); 3.0 (d, 2H); 2.55-2.45 (m, 2H); 2.1-2.0 (m, 4H).

MS (ES/+): m/z=295 $[MH]^+$.

Intermediate 27

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A solution of 2-bromo-5-fluorotoluene (10.8 mL) in anhydrous THF (40.5 mL) was dropped into a suspension of magnesium turning (2.2 g) and few crystals of iodine in anhydrous THF (21.5 mL) under a Nitrogen atmosphere. The mixture refluxed for 30 minutes, then it was allowed to cool to r.t. and added drop-wise to a mixture of intermediate **1** (8 g) and copper iodide (1.6 g) in anhydrous THF (66 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and stirred at 23°C for 1.5 hours. The mixture was cooled to 0°C, treated with 3M hydrochloric acid solution until pH=5 and extracted with AcOEt (3 x 100 mL). The combined organic extracts were washed with a saturated ammonium chloride solution (200 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (6.71 g) as a white foam.

T.l.c.: CH/AcOEt 8:2, Rf=0.17(detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.33 (dd, 1H); 7.07 (t, 1H); 7.0 (td, 1H); 4.48 (s, 1H); 3.99-3.81 (m, 4H); 2.72-2.53 (m, 4H); 2.46 (s, 3H); 1.86-1.74 (m, 2H); 1.36 (s, 9H); 0.94 (t, 3H).

MS (ES/+): m/z=427 $[M+Na]^+$.

Intermediate 28

4-Carboxymethyl-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate **27** (298 mg) in acetic acid (4.3 mL), conc. sulfuric acid (1.1 mL) and water (1.1 mL) was heated to 140°C for 5 hours. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (38 mL). Then, di-*tert*-butyl-dicarbonate (217.6 mg) was added and the resulting mixture was stirred at r.t. over week end. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=6-7 and then extracted with AcOEt (3 x 20 mL). The organic phase was washed with brine, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound (131 mg) as a white solid.

T.l.c.: CH/AcOEt 6:4, Rf=0.12 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 11.8 (bs, 1H); 7.28 (dd, 2H); 6.96 (dd, 1H); 6.91 (td, 1H); 3.4 (bm, 2H); 3.22 (bm, 2H); 2.7 (s, 2H); 2.47 (s, 3H); 2.1 (m, 2H); 2.01 (m, 2H); 1.37 (s, 9H).

MS (ES/+): m/z=374 $[M+Na]^+$.

Intermediate 29

4-{[(3,5-Dichlorobenzyl)methylcarbamoyl]methyl}-4-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (91 µL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (54.6 mg) were added to a solution of intermediate **28** (46 mg) in anhydrous DMF (3.8 mL) under a Nitrogen atmosphere. After stirring for 30 minutes, 3,5-dichlorobenzyl-methylamine hydrochloride (59.3 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt and washed with 5% sodium hydrogen carbonate and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 9:1 to 6:4) to give the title compound (34 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, Rf=0.16 (detection with ninhydrine).

IR (nujol, cm^{-1}): 1699 and 1643 (C=O).

NMR (d_6-DMSO): δ (ppm) 7.42 (dd, 1H); 7.24 (dd, 1H); 6.98 (d, 2H); 6.88 (dd, 1H); 6.83 (td, 1H); 4.26 (s, 2H); 3.45-3.08 (m, 4H); 2.23-1.99 (m, 4H); 2.81 (s, 3H); 2.58 (s, 2H); 2.41 (s, 3H); 1.33 (s, 9H).

MS (ES/+): m/z=545 $[M+Na]^+$.

Intermediate 30

4-{[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]methyl}-4-(4-fluoro-2-methyl-phenyl)-piperidine-1-carboxylic acid *tert*-butyl ester

DIPEA (241 µL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (144.4 mg) were added to a solution of intermediate **28** (122 mg) in anhydrous DMF (10 mL)

under a Nitrogen atmosphere. After stirring for 30 minutes, 3,5-bis(trifluorobenzyl)-methylamine hydrochloride (293.5 mg) was added. The mixture was stirred at r.t. for 2 hours, then it was diluted with AcOEt and washed with 5% sodium hydrogen carbonate and brine. The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 9:1 to 1:1) to give the title compound (159 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, Rf=0.1 (detection with ninhydrine).
IR (nujol, cm^{-1}): 1737 and 1638 (C=O).
NMR (d_6-DMSO): δ (ppm) 7.98 (s, 1H); 7.74 (s, 1H); 7.21 (dd, 1H); 6.87 (dd, 1H); 6.74 (td, 1H); 4.47 (s, 2H); 3.49 (m, 2H); 3.1 (m, 2H); 2.87 (s, 2H); 2.67 (s, 3H); 2.42 (s, 3H); 2.23 (m, 2H); 2.02 (m, 2H); 1.36 (s, 9H).
MS (ES/+): m/z=613 $[M+Na]^+$.

Intermediate 31

5-Ethoxycarbonyl-4-oxo-azepine-1-carboxylic acid *tert*-butyl

Ethyl diazoacetate (6.84 mL) and boron trifluoride diethyl etherate (6.34 mL) were added simultaneously over 1 hour to a suspension of *tert*-butyl-4-oxo-1-piperidine carboxylate (10.0 g) in dry Et2O (60 mL) previously cooled to -25°C under a Nitrogen atmosphere. The solution obtained was stirred at -25°C for 1 hour, then it was allowed to warm to 0°C and stirred at 0°C for 1 hour. The solution was treated with a saturated potassium carbonate solution (10 mL). The layers were separated; the organic phase was dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (petroleum/Et2O 6:4) to give the title compound (11.58 g) as a colourless oil.
T.l.c.: petroleum/Et2O 1:1, Rf=0.48 (detection with phosphomolybdic acid).
IR (nujol, cm^{-1}): 1744 and 1695 (C=O).
NMR (d_6-DMSO): δ (ppm) 4.08 (q, 3H); 3.82-3.64 (m, 2H); 3.38 (m, 2H); 2.64 (m, 2H); 1.9-1.64 (m, 2H); 1.36 (s, 9H); 1.16 (t, 3H).
MS (ES/+): m/z=286 $[MH]^+$.

Intermediate 32

Azepin-4-one hydrochloride

A suspension of intermediate **31** (11.58 g) in 3M hydrochloric acid (60 mL) was heated to reflux for 7 hours. The mixture was allowed to cool to r.t. and concentrated *in vacuo*. The residue was triturated with abs. EtOH (10 mL) to give the title compound (4.54 g) as a white solid.
M.p.: 189-191°C.
NMR (d_6-DMSO): δ (ppm) 9.17 (bs, 2H); 3.3 (m, 2H); 3.22 (m, 2H); 2.75 (m, 2H); 2.62 (m, 2H); 1.93 (m, 2H).

Intermediate 33

4-Oxo-azepine-1-carboxylic acid *tert*-butyl ester

Di *tert*-butyl dicarbonate (0.7 g) was added to a suspension of intermediate **32** (0.4 g) and TEA (0.45 mL) in anhydrous DCM (5 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was stirred for 1 hour at 0°C then it was allowed to reach r.t.. The mixture was treated with a saturated ammonium chloride solution (10 mL) and extracted with further DCM (2 x 10 mL). The combined organic extracts were washed with water, dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (528 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, Rf=0.3 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 3.53 (bm, 2H); 3.45 (bm, 2H); 2.58 (m, 2H); 2.52 (m, 2H); 1.61 (bm, 3H); 1.37 (s, 9H).

Intermediate 34

4-(1-Cyano-1-ethoxycarbonyl-methylene)-azepine-1-carboxylic acid *tert*-butyl ester

A round bottom flask equipped with a Dean Stark apparatus was charged with intermediate **33** (1.87 g), ethyl cyanoacetate (1.03 mL), methyl ammonium acetate (0.339 g) and acetic acid (0.5 mL) in anydrous benzene (15 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (10 mL). The aqueous layer was extracted with AcOEt (2 x 10 mL). The combined organic extracts were washed with a 1M sodium hydroxide solution (10 mL), dried and concentrated *in vacuo* to a residue, which was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (2.49 g – cis/trans mixture) as a colourless oil.

T.l.c.: CH/AcOEt 8:2, Rf=0.25 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 4.23 (q, 2H); 3.57 (t, 1H); 3.51 (t, 1H); 3.37 (m, 2H); 3.18 (t, 1H); 2.96 (m, 2H); 2.77 (m, 1H); 1.7 (m, 2H); 1.39-1.36 (m, 9H); 1.28-1.21 (m, 6H).

Intermediate 35

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluorophenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A solution of intermediate **34** (0.5 g) in anhydrous toluene (5 mL) was dropped over 30 minutes into a solution of 4-fluorophenyl magnesium bromide (2M in Et2O – 1.95 mL) in anhydrous Et2O (15 mL) previously cooled to 0°C under a Nitrogen atmosphere. The mixture was allowed to warm to r.t. and left at this temperature for 2 days. The mixture was treated with 3N sulfuric acid solution (5 mL), water (10 mL) and AcOEt (15 mL). The layers were separated and the aqueous phase was extracted with further AcOEt (2 x 15 mL). The combined organic layers were washed with a saturated sodium hydrogen carbonate (30 mL) and water (30 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (331 mg) as a colourless oil.

T.l.c.: CH/AcOEt 8:2, Rf=0.30 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.3 (m, 2H); 7.05 (m, 2H); 4.0 (bm, 2H); 4.2-2.5 (bm, 4H); 3.4 (s, 1H); 2.4-1.5 (bm, 6H); 1.4 (s + t, 12H).

Intermediate 36

4-Carboxymethyl-4-(4-fluorophenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate **35** (0.33 g) and a 15% potassium hydroxide solution in ethylene glycol (7 mL) was heated to 180°C overnight. The solution was allowed to cool to r.t., diluted with water (5 mL), cooled at 0°C and acidified with 15% hydrochloric acid until pH=1. The glycol-aqueous phase was distilled off (70°C/2 mbar) to leave a brown residue which was further dried (140°C/2 mbar for 1 hour) to give a mixture of 4-carboxymethyl-4-(4-fluorophenyl)-azepine and potassium chloride (700 mg).

Sodium hydroxide (24 mg) and di-*tert*-butyl-dicarbonate (60 mg) were added to a part of this material (80 mg) suspended in water (5 mL). The solution was stirred at r.t. overnight, then it was cooled to 0°C and treated with 0.1M hydrochloric acid solution until pH=1 and extracted with Et2O (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 1:1) to give the title compound (17 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.25 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.25 (m, 2H); 6.95 (t, 2H); 3.8-3.4 (m, 2H); 3.2 (m, 2H); 2.6 (s, 2H);2.5 (m, 3H); 2.3 (m, 1H); 2.0-1.5 (m, 2H); 1.4 (bs, 9H).

Intermediate 37

4-{[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]-methyl}-4-(4-fluorophenyl)-azepine-1-carboxylic acid *tert*-butyl ester

3,5-(Bis-trifluoromethyl-benzyl)-methylamine (14 mg), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10 mg) and 1-hydroxybenzotriazole (7 mg) were added to a solution of intermediate **36** (17 mg) in anhydrous DMF (2 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL), 0.005M hydrochloric acid solution (10 mL) and a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (18 mg) as a colourless oil.

T.l.c.: CH/AcOEt 6:4, Rf=0.4.

NMR (d_6-DMSO – 70°C): δ (ppm) 7.93 (bs, 1H); 7.78 (bs, 2H); 7.31 (m, 2H); 6.97 (bt, 2H); 4.51 (m, 2H); 3.51 (bm, 1H); 3.35 (bm, 1H); 3.15 (m, 2H); 2.71 (s, 3H); 2.7 (m, 2H); 2.48 (m, 1H); 2.26 (m, 1H); 2.04 (m, 1H); 1.87 (m, 1H); 1.69 (m, 1H); 1.51 (1H); 1.35 (s, 9H).

Intermediate 38

4-(1-Cyano-1-ethoxycarbonyl-methyl)-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A small amount of iodine and 3 drops of methyl iodide were added to a suspension of magnesium turnings (655 mg) in dry Et2O (15 mL), at r.t., under a Nitrogen atmosphere, then the mixture was vigorously refluxed. 2-Bromo-5-fluoro-toluene (3.1 mL) was added over 1 hour to this mixture followed by further Et2O (5 mL). The suspension was heated under vigorous reflux for 1.5 hours, then further Et2O (40 mL) was added. A solution of intermediate **34** (2.5 g) in anhydrous Et2O (10 mL) was added to the solution of Grignard so obtained over 30 minutes. The resulting solution was refluxed for further 30 minutes then it was cooled to 0°C, a 3M sulfuric acid solution (15 mL) and water (25 mL) were added and the aqueous layer was extracted with AcOEt (2 x 30 mL).

The combined organic extracts were washed with a saturated sodium hydrogen carbonate solution (50 mL) and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound (531 mg) as a white foam.

T.l.c.: CH/AcOEt 1:1, Rf=0.76 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 7.3 (m, 2H); 7.05 (m,2H); 4.0 (bm, 2H); 4.2-2.5 (bm, 4H); 3.4 (s, 1H); 2.4-1.5 (bm, 6H); 1.4 (s + t, 12H).

Intermediate 39

4-Carboxymethyl-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate **38** (0.531 g) in acetic acid (3 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C overnight. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (50 mL). Then, di-*tert*-butyl-dicarbonate (277 mg) was added and the resulting mixture was stirred at r.t. for 5 hours. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (60 mg) as a pale yellow oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.35 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 11.88 (bs, 1H); 7.3 (m, 1H); 6.99 (m, 1H); 6.91 (m, 1H); 3.6-3.0 (m, 4H); 2.6-2.4 (m, 2H); 2.45 (s, 3H); 2.6-2.4 (m, 2H); 2.05-1.9 (m, 2H); 1.8-1.4 (m, 2H); 1.3 (s, 9H).

Intermediate 40

4-{[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]-methyl}-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

DIPEA (43 μL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (34.3 mg) were added to a solution of intermediate **39** (30 mg) in anhydrous DMF (3 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-(bis-trifluoromethyl-benzyl)-methylamine hydrochloride (25.5 mg), was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL) and a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (30 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.4.

NMR (d_6-DMSO – 60°C): δ (ppm) 7.94 (s, 1H); 7.8 (s, 2H); 7.16 (m, 1H); 6.89 (m, 1H); 6.75 (m, 1H); 4.54 (s, 2H); 3.6-3.0 (m, 4H); 2.7 (s, 3H); 2.8-2.4 (m, 4H); 2.44 (s, 3H); 1.98 (m, 1H); 1.74 (m, 2H); 1.49 (m, 1H); 1.3 (bs, 9H).

Intermediate 41

4-{[(3,5-Dichlorobenzyl)methylcarbamoyl]-methyl}-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

DIPEA (34.3 μL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (34.3 mg) were added to a solution of intermediate **39** (30 mg) in anhydrous DMF (3 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-dichlorobenzyl-methylamine hydrochloride (20.5 mg) was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL) and a saturated sodium hydrogen carbonate solution (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 6:4) to give the title compound (30 mg) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.4.

NMR (d_6-DMSO): δ (ppm) 7.55-7.45 (m, 1H); 7.25-7.15 (m, 1H); 7.11 (s, 1H); 7.08 (s, 1H); 7.0-6.8 (m, 2H); 4.45-4.3 (m, 2H); 3.6-3.0 (m, 4H); 2.85-2.4 (m, 4H); 2.69 (s, 3H); 2.44 (s, 3H); 2.0-1.8 (m, 1H); 1.72 (m, 2H); 1.5-1.4 (m, 1H); 1.3 (bs, 9H).

Intermediate 42

3-Fluoro-4-oxo-piperidine-1-carboxylate *tert*-butyl ester

Trimethylsilyl trifluoromethanesulfonate (2.17 mL) was added to a solution of *tert*-butyl-4-oxo-1-piperidine carboxylate (2.0 g) and TEA (3.34 mL) in anhydrous DCM (20 mL) previously cooled to -30°C under a Nitrogen atmosphere. The mixture was stirred at this temperature for 1 hour, then it was quickly treated with cold saturated sodium hydrogen carbonate solution (20 mL). The layers were separated and the organic phase was dried and concentrated *in vacuo* to give 1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydro-4-pyridinyl-

trifluoromethanesulfonate as a yellow oil, which was dissolved in anhydrous acetonitrile (80 mL) and the resulting solution was treated with Selectfluor (3.89 g). The mixture was stirred at r.t. for 1 hour, then it was concentrated *in vacuo* and the residue was dissolved in AcOEt (50 mL). The organic layer was washed with a saturated sodium hydrogen solution (30 mL), dried and concentrated *in vacuo* to a residue, which was purified by chromatography on neutral Alumina Brochmann type 1 (initially AcOEt then AcOEt/MeOH 95:5) to give thetitle compound (0.99 g) as a colourless oil.

T.l.c.: CH/AcOEt 1:1, Rf=0.3.

NMR (d_6-DMSO): δ (ppm) 5.08 (dd, 1H); 4.32 (bm, 1H); 4.0 (bm, 1H); 3.19 (m, 2H); 2.56 (m, 1H); 2.36 (m, 1H); 1.43 (s, 9H).

Intermediate 43

5-Ethoxycarbonyl-3-fluoro-4-oxo-azepine-1-carboxylic acid *tert*-butyl ester

Ethyl diazoacetate (7.8 mL) and boron trifluoride diethyl etherate (7.2 mL) were added simultaneously over 50 minutes to a suspension of intermediate **42** (12.39 g) in dry Et2O (250 mL) previously cooled to -20°C under a Nitrogen atmosphere. The solution obtained was stirred at -20°C for 1 hour, then it was allowed to warm to 0°C, and treated with a saturated potassium carbonate solution (200 mL). The layers were separated and the organic phase was dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 9:1) to give the title compound (5.42 g) as a yellow oil.

T.l.c.: CH/AcOEt 85:15, Rf=0.1 (detection with ninhydrine).

NMR ($CDCl_3$): δ (ppm) 5.06 (dt, 1H); 4.3-4.1 (m, 2H); 3.53 (m, 1H); 4.0-3.2 (bs, 4H); 2.2-2.0 (m, 2H); 1.4 (s, 9H); 1.3-1.2 (t, 3H).

MS (ES/+): m/z=304 $[MH]^+$.

Intermediate 44

3-Fluoro-4-oxo-azepine-1-carboxylic acid, tert-butyl ester

A suspension of intermediate **43** (100 mg) in 3M hydrochloric acid (5 mL) was heated to reflux for 6 hours. The mixture was concentrated *in vacuo* to give the 3-fluoro-azepin-4-one hydrochloride (60.5 mg) as a whitish solid.

Di *tert*-butyl dicarbonate (86 mg) was added to a suspension of this compound (60.5 mg) and TEA (0.1 mL) in anhydrous DCM (5 mL) under a Nitrogen atmosphere. The mixture was stirred at r.t. overnight. The mixture was treated with a saturated ammonium chloride solution (10 mL) and extracted with further DCM (2 x 10 mL) The combined organic extracts were dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (50 mg) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.23 (detection with ninhydrine).

NMR (d_6-DMSO - 70°C): δ (ppm) 5.15 (dt, 1H); 3.76 (m, 2H); 3.53 (bm, 1H); 3.23 (bm, 1H); 2.54 (m, 1H); 2.43 (m, 1H); 1.71 (m, 1H); 1.64 (m, 1H); 1.35 (s, 9H).

Intermediate 45

4-(1-Cyano-1-ethoxycarbonyl-methyl)-3-fluoro-azepine-1-carboxylic acid *tert*-butyl ester

A round bottom flask equipped with a Dean Stark apparatus was charged with intermediate **44** (1.136 g), ethyl cyanoacetate (0.576 mL), methyl ammonium acetate (0.189 g) and acetic acid (0.281 mL) in anydrous benzene (9 mL). The mixture was heated to reflux overnight, then it was allowed to cool to r.t. and washed with water (20 mL). The aqueous layer was extracted with AcOEt (2 x 20 mL). The combined organic extracts were washed with 1M sodium hydroxide solution (20 mL) and a saturated ammonium chloride solution (20 mL), dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt 8:2) to give the title compound (0.873 g – cis/trans mixture) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.28 (detection with ninhydrine).

MS (ES/+): m/z= 326 $[MH]^+$.

Intermediate 46

4-(1-Cyano-1-ethoxycarbonyl-methyl)-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A small amount of iodine and 3 drops of methyl iodide were added to a suspension of magnesium turnings (215 mg) in dry Et2O (5 mL), at r.t., under a Nitrogen atmosphere, then the mixture was vigorously refluxed. 2-Bromo-5-fluoro-toluene (1.016 mL) was added over 1 hour to this mixture followed by further Et2O (2 mL). The suspension was heated under vigorous reflux for 1 hour. A solution of intermediate **45** (0.873 g) in anhydrous Et2O (3 mL) was added to the solution of Grignard so obtained over 30 minutes. The resulting mixture was refluxed for further 30 minutes then it was cooled to 0°C, a 3M sulfuric acid solution (3 mL) was added and the aqueous layer was extracted with AcOEt (2 x 30 mL).

The combined organic layers were washed with a saturated sodium hydrogen carbonate (30 mL) and water (15 mL), then dried and concentrated *in vacuo*. The residue was purified by flash chromatography (CH/AcOEt from 9:1 to 8:2) to give the title compound (308.4 mg) as a colourless oil.

T.l.c.: CH/AcOEt 8:2, Rf=0.21 (detection with ninhydrine).

NMR (d_6-DMSO - 70°C): δ (ppm) 7.34-7.27 (2m, 2H); 7.05-6.96 (bm, 2H); 5.8 (2bd, 1H); 4.58-4.33 (2s, 1H); 4.07 (m, 2H); 3.8-3.5 (bm, 2H); 3.4-3.0 (bm, 2H); 2.7-2.3 (bm, 1H); 1.8 (1.6 (bm, 1H); 1.8-1.6 (bm, 1H); 1.5-1.2 (bm, 1H); 1.23 (bs, 9H); 1.13-0.96 (2t, 3H).

MS (ES/+): m/z= 437 $[MH]^+$.

Intermediate 47

4-Carboxymethyl-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid *tert*-butyl ester

A mixture of intermediate **46** (0.29 g) in acetic acid (3 mL), conc. sulfuric acid (1 mL) and water (1 mL) was heated to 140°C for 6 hours. The solution was allowed to cool to r.t. and dropped into a 2.5M sodium hydroxide solution (30 mL). Then, di-*tert*-butyl-dicarbonate (145 mg) was added and the resulting mixture was stirred at r.t. overnight. It was cooled to 0°C and treated with 6M hydrochloric acid solution until pH=1 and then extracted with AcOEt (20 mL). The organic phase was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt from 8:2 to 6:4) to give the title compound (79.7 mg) as a pale yellow oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.18 (detection with ninhydrine).

NMR (d_6-DMSO - 70°C): δ (ppm) 11.64 (bs, 1H); 7.25 (dd, 1H); 6.96 (dd, 1H); 5.57 (dt, 1H); 3.78 (bm, 2H); 3.18 (bt, 2H); 2.83 (d, 1H); 2.68 (d, 1H); 2.47 (s, 3H); 2.33 (m, 1H); 2.09 (m, 1H); 1.79 (m, 1H); 1.59 (m, 1H); 1.31 (s, 9H).

MS (ES/+): m/z= 384 $[MH]^+$.

Intermediate 48

4-{[(3,5-Bis-trifluoromethyl-benzyl)methylcarbamoyl]-methyl}-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid, tert-butyl ester

DIPEA (50 µL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (37 mg) were added to a solution of intermediate **47** (34 mg) in anhydrous DMF (5 mL) under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-(bis-trifluoromethyl-benzyl)-methylamine hydrochloride (28.7 mg), was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 7:3) to give the title compound (37.1 mg) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.19.

NMR (d_6-DMSO): δ (ppm) 8.04-7.88 (2bs, 1H); 7.77-7.72 (2bs, 2H); 7.12 (m, 1H); 6.91 (m, 1H); 6.73 (m, 1H); 5.8-5.62 (2bd, 1H); 4.8-4.4 (m, 2H); 3.9-3.5 (bm, 2H); 3.13 (bm, 2H); 2.92 (bm, 2H); 2.83-2.81 (2bs, 3H); 2.44-2.42 (2bs, 3H); 2.35-2.0 (bm, 2H); 1.67 (bm, 1H); 1.48 (bm, 1H); 1.28 (s, 9H).

Intermediate 49

4-{[(3,5-Dichlorobenzyl)methylcarbamoyl]-methyl}-3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepine-1-carboxylic acid, tert-butyl ester

DIPEA (50 µL) and O-(benzotriazol-1-yl)-N,N,N'N'-tetramethyluronium tetrafluoroborate (36.2 mg) were added to a solution of intermediate **47** (33.2 mg) in anhydrous DMF (5 mL)

under a Nitrogen atmosphere. After stirring for 10 minutes, 3,5-dichlorobenzyl-methylamine hydrochloride (21.6 mg), was added. The mixture was stirred at r.t. overnight, then it was diluted with AcOEt (10 mL) and washed with water (10 mL). The organic layer was dried, concentrated *in vacuo* and the residue was purified by flash chromatography (CH/AcOEt 75:25) to give the title compound (38.4 mg) as a colourless oil.

T.l.c.: CH/AcOEt 7:3, Rf=0.21.

NMR (d_6-DMSO): δ (ppm) 7.49-7.42 (2t, 1H); 7.13 (m, 1H); 7.02 (d, 2H); 6.85 (m, 2H); 5.81-5.65 (2bd, 1H); 4.41-4.28 (2m, 2H); 3.9-3.5 (m, 2H); 3.08 (bm, 2H); 2.86 (m, 2H); 2.72-2.7 (2s, 3H); 2.41-2.4 (2s, 3H); 2.35-2.0 (bm, 2H); 1.65 (bm, 1H); 1.45 (bm, 1H); 1.25 (s, 9H).

Example 1

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide hydrochloride

TFA (0.5 mL) was added to a solution of intermediate **4** (80 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 1:1 containing 0.5% of conc. ammonium hydroxide solution) to give the N-(3,5-dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide (40 mg) as a pale yellow oil (T.l.c.: AcOEt/MeOH 1:1 containing 0.5% of conc. NH4OH, Rf=0.03).

This compound (40 mg) was dissolved in anhydrous Et2O (1 mL) and treated with hydrochloric acid (1M in Et2O – 0.195 mL) at 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound (40 mg) as a white solid.

NMR (d_6-DMSO – 70°C): δ (ppm) 8.48 (bs, 2H); 7.52-7.47 (2bs, 1H); 7.41 (m, 2H); 7.15-7.11 (2t, 2H); 7.02-7.0 (2s, 2H); 4.29-4.19 (s, 2H); 3.21 (m, 2H); 2.88 (m, 2H); 2.79-2.75 (2s, 3H); 2.54 (s, 3H); 2.4-2.2 (m, 4H).

Example 2

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide hydrochloride

TFA (0.5 mL) was added to a solution of intermediate **9** (60 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with

DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the N-(3,5-dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide (45 mg) as a pale yellow oil (T.l.c.: AcOEt/MeOH 8:2, Rf=0.1).

This compound was dissolved in anhydrous Et2O (1 mL) and treated with hydrochloric acid (1M in Et2O – 0.21 mL) at 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound (42 mg) as a white solid.

NMR (d_6-DMSO – 70°C): δ (ppm) 8.95 (bs, 2H); 7.46 (m, 2H); 7.39 (bs, 1H); 7.13 (t, 2H); 6.99 (bs, 2H); 5.86 (bd, 1H); 4.3 (m, 2H); 3.48 (m, 1H); 3.18 (m, 1H); 2.99 (m, 1H); 2.94 (d, 1H); 2.76 (d, 1H); 2.75 (m, 1H); 2.69 (m, 1H); 2.66 (s, 3H); 2.27 (bm, 1H).

Example 3

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

Hydrochloric acid (4M in dioxan – 0.21 mL) was added to a solution of intermediate **17** (35 mg) in anhydrous DCM (2 mL) previously cooled to -5°C under a Nitrogen atmosphere. The solution was allowed to warm to r.t. and stirred at r.t. for 30 hours, then it was concentrated *in vacuo* and the residue was purified by flash chromatography (from CH/AcOEt 6:4 to MeOH) to give 4-(4-fluorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide (18 mg).

This material was dissolved in Et2O (1 mL), cooled to -0°C and treated with hydrochloric acid (4M in Et2O – 72 µL). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* to give the title compound (18 mg) as a white solid.

NMR (d_6-DMSO – 70°C): δ (ppm) 8.66 (bm, 2H); 7.94 (bs, 1H); 7.72 (bs, 2H); 7.32 (dd, 2H); 7.17 (t, 2H); 4.65 (s, 2H); 3.28 (m, 2H); 3.1 (m, 2H); 2.62 (s, 3H); 2.52 (m, 2H); 2.14 (m, 2H).

MS (ES/+): m/z=463 $[MH\text{-}HCl]^+$.

Example 4

4-(4-Chlorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide hydrochloride

Hydrochloric acid (4M in dioxan – 86 µL) was added to a solution of intermediate **22** (15 mg) in anhydrous DCM (0.2 mL) previously cooled to -5°C under a Nitrogen atmosphere. The solution was allowed to warm to r.t. and stirred at r.t. for 30 hours, then it was concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 7:3) to give 4-(4-

chlorophenyl)-piperidine-4-carboxylic acid (3,5-bis-trifluoromethyl-benzyl)-methylamide (11 mg).

This material was dissolved in Et2O (1 mL), cooled to -0°C and treated with hydrochloric acid (4M in Et2O – 54 µL). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* to give the title compound (10.3 mg) as a beige solid.

NMR (d_6-DMSO – 70°C): δ (ppm) 8.8 (bm, 1H); 7.92 (s, 1H); 7.71 (s, 2H); 7.39 (d, 2H); 7.28 (d, 2H); 4.63 (s, 2H); 3.26 (m, 2H); 3.0 (m, 2H); 2.61 (s, 3H); 2.5 (m, 2H); 2.15 (m, 2H).

MS (ES/+): m/z=479 $[MH\text{-}HCl]^+$.

Example 5

4-(4-Fluorophenyl)-piperidine-4-carboxylic acid (3,5-dichloro-benzyl)-methylamide hydrochloride

TFA (3.2 mL) was added to a solution of intermediate **23** (80 mg) in anhydrous DCM (13 mL) previously cooled to -0°C under a Nitrogen atmosphere. The solution was stirred at -0°C for 18 hours, then it was concentrated *in vacuo*. The residue was dissolved in AcOEt (30 mL) and washed with saturated sodium carbonate solution (20mL). The organic layer was dried and concentrated in vacuo to a residue which was purified by flash chromatography (first AcOEt then MeOH) to give 4-(4-fluorophenyl)-piperidine-4-carboxylic acid (3,5-dichloro-benzyl)-methylamide (27 mg).

This material was dissolved in Et2O (2 mL), cooled to -0°C and treated with hydrochloric acid (4M in Et2O – 140 µL). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* to give the title compound (22.5 mg) as a beige solid.

NMR (d_6-DMSO – 70°C): δ (ppm) 8.66 (bs, 2H); 7.44 (t, 1H); 7.33 (dd, 2H); 7.29 (t, 2H); 7.1 (s, 2H); 4.46 (s, 2H); 3.27 (m, 2H); 3.1 (m, 2H); 2.58 (s, 3H); 2.5 (m, 2H); 2.13 (t, 2H).

MS (ES/+): m/z=395 $[MH\text{-}HCl]^+$.

Example 6

N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (1.9 mL) was added to a solution of intermediate **30** (144 mg) in anhydrous DCM (2.5 mL) under a Nitrogen atmosphere. The solution was stirred at 23°C for 3 hours, then it was diluted with DCM and washed with saturated potassium carbonate solution and brine. The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (from AcOEt/MeOH 1:1 to AcOEt/MeOH 3:7 + 3% NH4OH, then MeOH + 4% NH4OH) to give the title compound (94 mg) as colourless oil.

T.l.c.: AcOEt/MeOH 1:1 + 1%NH4OH, Rf=0.08 (detection with ninhydrine).

NMR (d_6-DMSO): δ (ppm) 7.98 (bs, 1H); 7.74 (bs, 2H); 7.17 (dd, 1H); 6.84 (dd, 1H); 6.7 (dt, 1H); 4.46 (s, 2H); 2.83 (s, 2H); 2.79 (bt, 2H); 2.62 (s, 3H); 2.56 (bt, 2H); 2.41 (s, 3H); 2.15 (m, 2H); 1.97 (m, 2H).
MS (ES/+): m/z=491 $[M+H]^+$.

Example 7
N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide

TFA (0.4 mL) was added to a solution of intermediate **29** (30 mg) in anhydrous DCM (0.5 mL) under a Nitrogen atmosphere. The solution was stirred at 23°C for 1 hour, then it was diluted with DCM and washed with saturated potassium carbonate solution and brine. The organic layer was dried and concentrated *in vacuo* to a residue which was purified by flash chromatography (from AcOEt/MeOH 1:1 to AcOEt/MeOH 3:7 + 3% NH4OH) to give the title compound (23.5 mg) as colourless oil.
T.l.c.: AcOEt/MeOH 3:7 + 3%NH4OH, Rf=0.12 (detection with ninhydrine).
NMR (d_6-DMSO): δ (ppm) 7.45 (s, 1H); 7.25 (dd, 1H); 7.02 (s, 2H); 7.0-6.8 (m, 2H); 4.28 (s, 2H); 2.81-2.78 (s + m, 4H); 2.55-2.57 (m, 5H); 2.43 (s, 3H); 2.17 (m, 2H); 1.99 (m, 2H).
MS (ES/+): m/z=423 $[M+H]^+$.

Example 8
N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide hydrochloride

The compound of Example 7 (19 mg) was dissolved in Et2O (0.2 mL), cooled to 0°C and treated with hydrochloric acid (1M in Et2O – 54 μL). The mixture was stirred at 0°C for 10 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane to give the title compound (19.3 mg) as a white solid.

NMR (d_6-DMSO): δ (ppm) 8.46 (bd, 2H); 7.4 (s, 1H); 7.3 (m, 1H); 7.02 (s, 2H); 6.94 (m, 2H); 4.31 (s, 2H); 3.23-2.9 (m, 4H); 2.88 (m, 2H); 2.63 (s, 3H); 2.5 (s, 3); 2.5-2.3 (m, 4H).

Example 9
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide hydrochloride

TFA (0.5 mL) was added to a solution of intermediate **37** (16 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give N-(3,5-bis-

trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide (12 mg - T.l.c.: DCM/MeOH 8:2 + 0.5% NH4OH, Rf=0.4).

This compound (12 mg) was dissolved in anhydrous Et2O (1 mL) and treated with hydrochloric acid (1M in Et2O – 0.05 mL) at 0°C under a Nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes, then it was concentrated *in vacuo* and the residue was triturated with pentane (2 x 1 mL) to give the title compound (10 mg) as a white solid.
NMR (d_6-DMSO): δ (ppm) 8.41 (bs, 2H); 7.92 (s, 1H); 7.74 (s, 2H); 7.33 (dd, 2H); 7.01 (bt, 2H); 4.5 (m, 2H); 3.27 (dd, 1H); 3.07 (m, 2H); 2.91 (dd, 1H); 2.72 (bs, 3H); 2.81-2.65 (m, 2H); 2.56 (m, 1H); 2.42-2.29 (m, 2H); 2.05 (dd, 1H); 1.86 (bm, 1H); 1.6 (bm, 1H).

Example 10

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide

TFA (0.5 mL) was added to a solution of intermediate **40** (30 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give the title compound (17 mg) as a pale yellow oil.
T.l.c.: DCM/MeOH 8:2, Rf=0.5.
NMR (d_6-DMSO): δ (ppm) 8.06-8.0 (2bs, 1H); 7.8-7.76 (2bs, 2H); 7.23-7.15 (2m, 1H); 6.91 (m, 1H); 6.76 (m, 1H); 4.69 (bs, 1H); 4.53 (m, 1H); 3.0-2.3 (m, 11H); 2.43 (s, 3H); 2.01 (m, 2H); 1.66 (m, 1H); 1.41 (m, 1H).

Example 11

N-(3,5-Dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide

TFA (0.5 mL) was added to a solution of intermediate **41** (30 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (2 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (DCM/MeOH 8:2) to give the title compound (20 mg) as a pale yellow oil.
T.l.c.: DCM/MeOH 8:2, Rf=0.5.

NMR (d_6-DMSO): δ (ppm) 7.53-7.47 (2t, 1H); 7.24-7.2 (2dd, 1H); 7.1 (d, 2H); 6.88 (m, 2H); 4.46-4.34 (s + m, 2H); 3.0-2.3 (m, 11H); 2.44 (s, 3H); 2.01 (m, 2H); 1.67 (bm, 1H); 1.39 (bm, 1H).

Example 12

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide

TFA (0.5 mL) was added to a solution of intermediate **48** (35 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (4 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the title compound (25.1 mg) as a pale yellow oil.

T.l.c.: AcOEt/MeOH 8:2, Rf=0.14.

NMR (d_6-DMSO): δ (ppm) 8.06-7.97 (2bs, 1H); 7.76 (bs, 2H); 7.17-7.13 (2dd, 1H); 6.89 (dd, 1H); 6.78 (dt, 1H); 5.53-5.4 (2bd, 1H); 4.76-4.53 (2m, 2H); 3.25-2.85 (m, 4H); 2.68 (m, 2H); 2.91-2.72 (2s, 3H); 2.44-2.28 (2s, 3H); 2.2 (m, 2H); 1.57 (bm, 1H); 1.3 (bm, 1H).

Example 13

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide

TFA (0.5 mL) was added to a solution of intermediate **49** (36.1 mg) in DCM (2 mL) under a Nitrogen atmosphere. The resulting solution was stirred at r.t. for 30 minutes, then a saturated potassium hydroxide solution was added until pH=9. The aqueous layer was extracted with DCM (4 x 15 mL). The combined organic extracts were dried, concentrated *in vacuo* and the residue was purified by flash chromatography (AcOEt/MeOH 8:2) to give the title compound (20.5 mg) as a pale yellow oil.

T.l.c.: AcOEt/MeOH 8:2, Rf=0.08.

NMR (d_6-DMSO): δ (ppm) 7.54-7.46 (2t, 1H); 7.16 (m, 1H); 7.11-7.07 (2d, 2H); 6.94 (dd, 1H); 6.87 (m, 1H); 5.6-5.49 (2bd, 1H); 4.55-4.35 (2m, 2H); 3.25-2.88 (m, 2H); 3.05 (m, 2H); 2.85-2.69 (2s, 3H); 2.7 (m, 1H); 2.65-2.35 (m, 1H); 2.46 (2s, 3H); 2.35-2.1 (m, 2H); 1.62-1.5 (2bm, 1H); 1.33-1.23 (bm, 1H).

Example 14

N-(3,5-Dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide (14a isomer1)and (14b isomer 2)

The compound of example **13** (16 mg) was separated into the enantiomers via preparative HPLC (Column: Chiralpack AD 25 x 2 cm; mobile phase: n-hexane/EtOH 8:2; flux=7.5 mL/min; λ=225 nm). Thus, example **14a** (6 mg) and example **14b** (5.8 mg) were obtained.

Example 14a:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 8:2, flux=1 mL/min, λ=225 nm; retention time 12.2 minutes. Ratio **14a/14b**=100:0.

Example 14b:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 8:2, flux=1 mL/min, λ=225 nm; retention time 14.05 minutes. Ratio **14a/14b**=0:100.

Example 15

N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide (15a isomer 1)-and (15b isomer 2)

The compound of example **12** (21 mg) was separated into the enantiomers via preparative HPLC (Column: Chiralpack AD 25 x 2 cm; mobile phase: n-hexane/EtOH 92:8; flux=7.5 mL/min; λ=225 nm). Thus, example **15a** (4.9 mg) and example **15b** (6.6 mg) were obtained.

Example 15a:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 85:15, flux=1 mL/min, λ=225 nm; retention time 7.37 minutes. Ratio **15a/15b**=96:4.

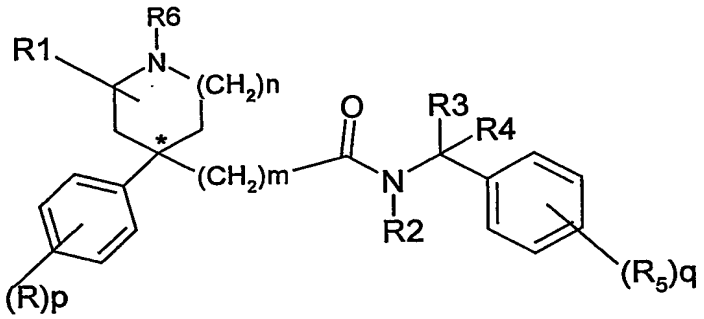
Example 15b:

Chiral HPLC: Column Chiralpack AD 25cm x 4.6mm x 5μ, mobile phase n-hexane/EtOH 92:8, flux=1 mL/min, λ=225 nm; retention time 8.04 minutes. Ratio **15a/15b**=2:98.

The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

Claims

1. A compound of formula (I)



(I)

wherein

R represents halogen , C_{1-4} alkyl, trifluoromethyl or trifluoromethoxy;

R_1 represents hydrogen, halogen , cyano, C_{1-4} alkyl optionally substituted by halogen, cyano, C_{1-4} alkoxy ;

R_2 represents hydrogen, or a C_{1-4} alkyl group;

R_3 and R_4 independently represent hydrogen, C_{1-4} alkyl or R_3 together with the R_4 represents C_{3-7} cycloalkyl;

R_5 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_6 represents hydrogen or (CH2)rR_7;

R_7 represents hydrogen, C_{3-7} cycloalkyl, C_{1-4} alkoxy, amine, C_{1-4} alkylamine, $(C_{1-4}$ alkyl$)_2$amine, OC(O)NR_9R_8 or C(O)NR_9R_8;

R_9 and R_8 independently represent hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl;

m represents zero or an integer from 1 to 4;

n represents 1 or 2;

p is an integer from 1 to 3;

q are independently zero or an integer from 1 to 3;

r is an integer from 1 to 4;

and pharmaceutically acceptable salts and solvates thereof.

2. A compound selected from:

N-(3,5-dichlorobenzyl)-2-[4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;

N-(3,5-dichlorobenzyl)-2-[3-fluoro-4-(4-fluorophenyl)-piperidin-4-yl]-N-methyl-acetamide;

4-(4-fluorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;

4-(4-chlorophenyl)-piperidine-4-carboxylic acid, (3,5-bis-trifluoromethyl-benzyl)-methylamide;

4-(4-fluorophenyl)-piperidine-4-carboxylic acid, (3,5-dichloro-benzyl)-methylamide;

N-(3,5-Bis-trifluoromethyl)-benzyl-2-[(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide;
N-(3,5-dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-piperidin-4-yl]-N-methyl-acetamide
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluorophenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-dichlorobenzyl)-2-[4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-dichlorobenzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-N-methyl-acetamide;
N-(3,5-Bis-trifluoromethyl-benzyl)-2-[3-fluoro-4-(4-fluoro-2-methyl-phenyl)-azepin-4-yl]-methyl-acetamide
and pharmaceutically acceptable salt thereof.

3. A compound as claimed in claim 1 or 2 for use in therapy.

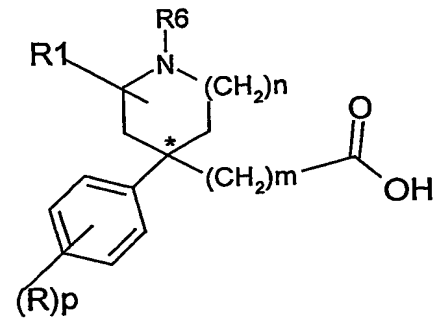
4. The use of a compound as claimed in claim 1 or 2 in the preparation of a medicament for use in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

5. The use of a compound as claimed in claim 1 or 2 in the treatment of conditions mediated by tachykinins (including substance P and other neurokinins) and/or by selective inhibition of the serotonin reuptake transporter protein.

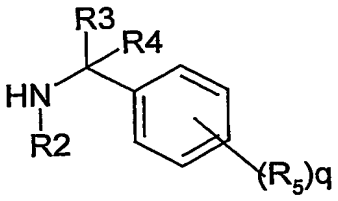
6. A pharmaceutical composition comprising a compound as claimed in claim 1 or 2 in admixture with one or more pharmaceutically acceptable carriers or excipients.

7. A method for the treatment of a mammal, including man, in particular in the treatment of conditions mediated by tachykinins, including substance P and other neurokinins and/or by selective inhibition of the serotonin reuptake transporter protein.
comprising administration of an effective amount of a compound of formula (I) as claimed in claim 1 or 2.

8. A process for the preparation of a compound as claimed in claim 1 or 2, which comprises reacting an activated derivative of the carboxylic acid of formula (II) wherein R_6 is nitrogen protecting group or (CH2)rR_7 , with amine (III)



(II)



(III)

followed where necessary or desired by one or more of the following steps

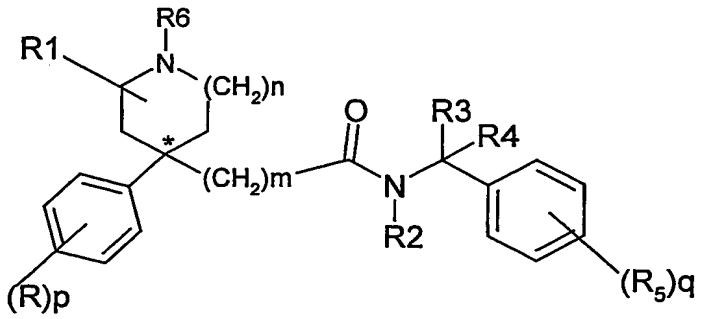
i) removal of any protecting group;

ii) isolation of the compound as a salt or a solvate thereof;

iii) separation of a compound of formula(I) or derivative thereof into the enantiomers thereof.

Abstract

The present invention relates to piperazine derivatives of formula (I)



(I)

wherein

R represents halogen , C_{1-4} alkyl, trifluoromethyl or trifluoromethoxy;

R_1 represents hydrogen, halogen , cyano, C_{1-4} alkyl optionally substituted by halogen, cyano, C_{1-4} alkoxy ;

R_2 represents hydrogen, or a C_{1-4} alkyl group;

R_3 and R_4 independently represent hydrogen, C_{1-4} alkyl or R_3 together with the R_4 represents C_{3-7} cycloalkyl;

R_5 represents trifluoromethyl, C_{1-4} alkyl, C_{1-4} alkoxy, trifluoromethoxy or halogen;

R_6 represents hydrogen or (CH2)rR_7;

R_7 represents hydrogen, C_{3-7} cycloalkyl, C_{1-4} alkoxy, amine, C_{1-4} alkylamine, (C_{1-4} alkyl)$_2$amine, OC(O)NR_9R_8 or C(O)NR_9R_8;

R_9 and R_8 independently represent hydrogen, C_{1-4} alkyl or C_{3-7} cycloalkyl;

m represents zero or an integer from 1 to 4;

n represents 1 or 2;

p is an integer from 1 to 3;

q are independently zero or an integer from 1 to 3;

r is an integer from 1 to 4;

and pharmaceutically acceptable salts and solvates thereof, process for their preparation and their use in the treatment of condition mediated by tachykinins and/or by selective inhibition of serotonin reuptake transporter protein.